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Are we sure about the evidence for zinc in prophylaxis of the common cold?

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Response to: Singh M, Das RR. Clinical potential of zinc in prophylaxis of the common cold. *Expert Rev. Respir. Med.* 5(3), 301–303 (2011).

In their article on the potential of zinc in prophylaxis of the common cold [1], Singh and Das report on evidence from clinical trials and meta-analyses. The authors cite their recent Cochrane systematic review [2], showing statistically significant evidence for the efficacy of the prophylactic use of zinc for the common cold. We feel that a little more clarity is needed on the results presented by Singh and Das from their Cochrane review [2] to allow readers a critical understanding of the evidence presented. First, the three results reported in their article (incidence rate ratio, child absenteeism from school and antibiotic prescription) are all based on the findings from just two studies (Kurugol *et al.* [3] and Vakili *et al.* [4]) even though six studies (including two by McElroy *et al.* [5,6]) are described by Singh and Das. Such selective reporting may fail to give an overview of all of the evidence and counteracts the core principle of undertaking a systematic review.

Second, as we have detailed elsewhere [101], we have a number of concerns regarding the validity of the results of the Cochrane review undertaken by Singh and Das [2]. In particular, we believe that the potential for biases in their review were not fully considered, and so their findings may overestimate the efficacy of zinc for the common cold. We found that this was particularly likely for their primary outcomes of duration and severity of symptoms using contour-enhanced funnel plots (Figure 1) [7]. Although the plots contain relatively small numbers of studies there is a concerning trend in both graphs that as the size of the trial decreases, the effect sizes observed become increasingly large. Additionally, the most precise studies (towards the top of the plots) have effect sizes that are either zero or very close to it. One possible explanation, and we acknowledge that this is not the only explanation, for such 'small study effects' trends is publication bias, which would imply that outcomes from trials with less beneficial/harmful effects have been suppressed. This could be owing to the suppression of whole trials that have never been published or it could be owing to the suppression of particular outcomes from certain trials (outcome reporting bias) [8], or a combination of the two. When evidence of small study effects is found, the Cochrane handbook (Section 10.4.4 [9]) recommends conducting sensitivity analyses examining how the results of the meta-analysis change under different assumptions relating to the reasons for these effects. In their Cochrane review, Singh and Das mention that they assessed the likelihood of small study effects [2], such as publication bias, by examining the funnel plot for asymmetry. However, there is no further mention or discussion of the results of such investigation in the Cochrane review.

For the three outcomes reported in [1], an assessment of such biases cannot be undertaken as there are only two studies. However, given that we have these concerns for the primary outcomes of the Cochrane review it is reasonable to consider such concerns for the three outcomes reported in [1]: that studies showing less beneficial effects have not been published and so the efficacy (measured here by incidence rate ratio, child absenteeism from school and antibiotic prescription) of zinc for the common cold has been overestimated.

In light of the above, we are concerned that the potential threats of such biases in

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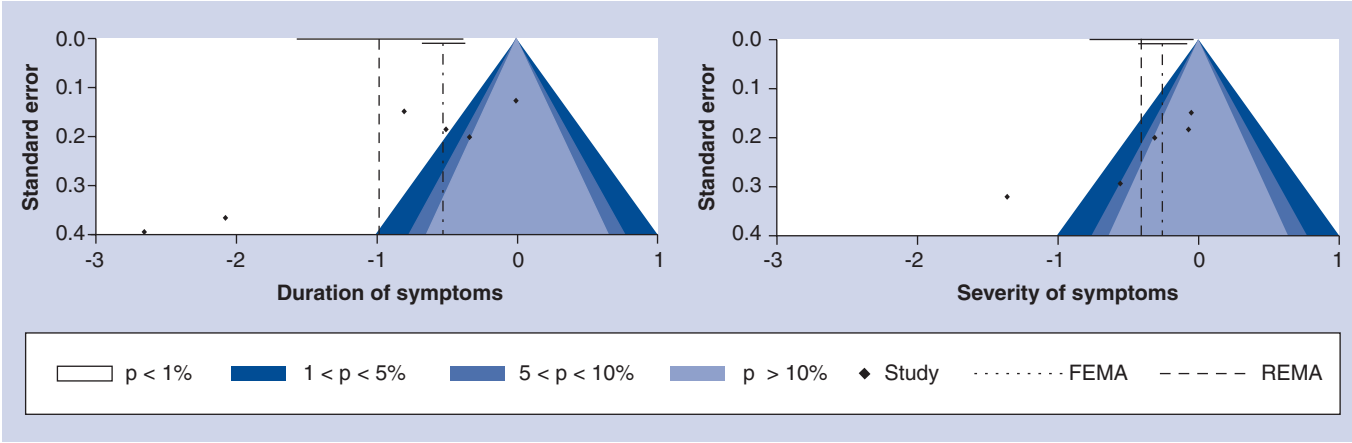

Figure 1. Funnel plots for the two primary treatment outcomes in the Cochrane review.
FEMA: Fixed effects-meta-analysis; REMA: Random-effects meta-analysis.
Data taken from [101].

the review have not been considered carefully enough. We therefore feel that readers should be cautious in their interpretation of the evidence presented in [1] owing to the possible threat of reporting and publication biases on the results of their Cochrane review.

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